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20th.February,1952.

Dear Dr.Lederberg,

Thank you for your last air-letter of January 7,telling me your findings on the relation of lambda to recombination,which probably saved me much work as I would have otherwise have felt obliged to exclude lambda myself as the agent. Since I do not have any technical assistance this would have occupied a considerable amount of my time. I must apologise for not having written to you since,but I thought I would wait until I had some information to give you,and until my reprints were ready to send. I now enclose 6 reprints of the 'streptomycin' article,together with a typescript of another letter to Nature on the differential action of UV light. As a result of these findings of mine I considered it reasonable to adopt,as a working hypothesis,the view that W677 accepted but did not liberate a gamete while the majority of cells in 58-161 cultures behaved in the opposite manner. Cavalli's finding that W 677,unlike K 12(wild type),58-161 and prototrophs,was not interfertile tended to confirm this view,as did my confirmation of Cavalli's finding that prototrophs having the W 677 phenotype of marker characters can recombine readily with W 677,and that the fertility of such prototrophs could be enhanced by UV in the same manner as 58-161. It seemed to me that interfertility in gene donator cultures could best be explained by supposing that a small proportion of the population of such cultures became gene acceptors by spontaneously losing their gametes. This appears to happen in populations of bacteria which carry latent phage,a good example being the reversion of Salm.typhi type F_2 to type F_1 through complete loss of the latent phage which appears to determine the type specificity of Vi antigen,as has recently been shown by Felix and Anderson. This naturally led to the idea that the K 12 gamete might be an"infective" agent - i.e.a self-reproducing product of meiosis which existed in the same sort of relationship with the cell as does latent phage but which did not disorganise the metabolism of the cell which it infects. In an attempt to isolate an infertile strain of 58-161 in order to test this hypothesis,I examined 140 58-161 colonies but all proved capable of recombination with W 677. I then heard that the same pair of mutants in the possession of Dr.C.C.Spicer (Central Public Health Laboratory,Colindale,London,N.W.9),which had previously recombined normally,showed no recombination after being kept for a year on egg medium in the refrigerator. They behaved as predicted,

Spicer's W677 strain recombining normally with my 58-161,but his 58-161 failing to form prototrophs with my W 677,even after treatment with UV. I then found that Spicer's 58-161 behaved as a gene acceptor in an identical manner to W 677,in that it recombined with wild-type K 12(using streptomycin) and with all prototrophs which formed prototrophs with W 677,but not with one prototroph which did not. I then attempted to make 58-161/Spicer into a fertile gene donator by marking it with S^r and Az^r,growing it [redacted] in broth with UV-treated fertile 58-161 and then plating on S-agar and testing 25 S^rAz^r [redacted] colonies for ability to recombine with W 677. I have done this twice and on each occasion 7/25 colonies have been fertile. I assume that if the genotype of the two strains had differed these "re-fertilised" 58-161/Spicer strains would constitute recombinants,from which it might be inferred that the true recombination rate is really extremely high. I have also grown W 677/S^r with fertile 58-161 under the same conditions and obtained 10/16 colonies capable of recombining with infertile 58-161/Spicer. I consider this is very strong evidence that the K 12 gamete behaves like an infective agent. I think that the absence of the gamete in filtrates (or even in centrifuged supernatants - see enclosed typescript) can be explained by the fact that the gamete has the same specificity for the bacterial surface as phage has and remains adsorbed to it after liberation. After all,the only reason why phage is filterable is that it destroys the cell which harbours it. In this way contact between a gene donator and acceptor cell would be necessary for transfer. It may be that a small number of gametes are in fact liberated free but cannot be demonstrated by the usual recombination technique. Do!nt you think that this question of filterability might be approached afresh by the "infectivity" technique which yields such a high rate of infection? Incidentally,up till recently I have been using logarithmic phase broth cultures of my mutants and usually obtained a fertility enhancement of X 5 to X 20 after UV. I then tried the effect of UV on overnight agar cultures and obtained enhancements of over X 200 on three consecutive occasions. I think this must be due, not to increased UV liberation in old cultures, but to greatly diminished natural liberation of the gamete. I only have a smattering of genetics and do not know whether the high "infection" rate and the low normal recombination rate as tested for by the usual selective techniques are compatible with the idea that the infective agent is,in fact,a complete gamete. This is,perhaps,too simple a conception.

I fear this is rather a rambling and "wooly" letter but I find it hard to express myself clearly directly on a typewriter. I hope to publish some of these results in Nature and then get down to the difficult business of writing it up properly and in detail.

With kind regards, Yours sincerely,

William Hayes

(Dr.William Hayes)

P.S. A letter has just arrived from Cavalli by the afternoon post,telling me that you have demonstrated infectivity a months ago! It's extraordinary how these things happen all at once. Please let me know your views about publication. It is interesting that you,Cavalli and myself,all working from,presumably,a different point of view should have arrived at the same broad conclusion.